Corrected Cerebral Flow Reserve from Brain SPECT as a Marker of Dementia Risk

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Background: Mixed Dementia (including Alzheimer's) risk may be increased by hypertension (BP), diabetes mellitus (DM), waist-height ratio (WH), traumatic brain injury (TI), thyroid (Td), renal (Rd), pituitary (Pd) disease and depression (De). To study dementia pathogenesis we developed a brain SPECT measure of cerebral flow reserve (CFi) with correction factors due to decreased tracer clearance in Rd.

Methods: Outpatients age 22 to 93 yrs had mainly mild cognitive impairment by MMSE or Test Your Memory tests. Brain SPECT included basal, perfusion-stimulated (e.g. 500 mg acetazolamide IV) and post therapy (e.g. 1.2 mg liraglutie sq) with Tc-99m-HMPAO or Tc-99m-ECD.. Cortical metabolic and perfusion indices (CMi, CPi) were calculated from basal and perfusion-stimulated SPECT. CFi = CPi—CMi was corrected by a flat 3% decrease, or from multicompartment analysis, for GFR < 60 ml/min (MDRD formula). De was defined by clinical exam. Hypertensive was untreated BP > 140/90, but treated before brain SPECT as was Td. Pd were treated if post hypophysectomy or post drug therapy.

Results: CFi = CPi - CMi was (5+-2)% for patients with low likelihood of disease, and CFi < 1% was the lower limit of normal. Ages were similar among the groups. CFi was low in 90% of Pd (47/52), 59% (80/135) of BP, 57% (43/75) of DM, 67% of De (35/52), 66% of Td (71/107) and 61% (56/92) of Rd, but only 30% in Rd (28/92) if FRi uncorrected. Most, 87% of Pd (55/63) had hypothalamic defects; 68% of Pd (43/63) had orbitofrontal defects, of whom 42% or (18/43) had De. Stroke or TIA occurred in 31% of PD (19/62), 30% of Rd (22/74) and 28% of DM (21/75). Most successful results were 68% of Pd (13/22) with normal CFi post-therapy.

Conclusion: Particularly low CFi in Pd suggests a fundamental role of an intact neuroendocrine system to maintain CFi and prevent dementia. Moreover, effective endocrine therapy to improve CFi or prevent its age-related decline could be part of a more comprehensive set of specific therapies to decrease dementia risk. Clinical depression with such a multimodality approach will likely be significant and a key issue in quality of care.

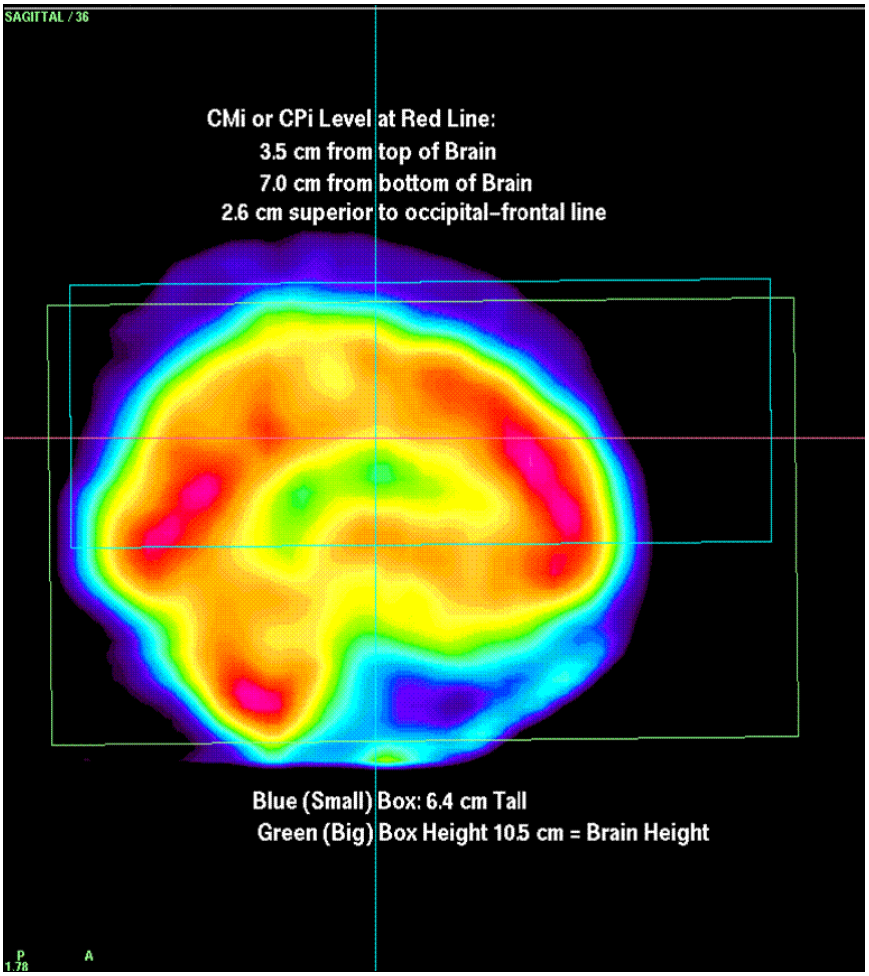

Fig. A. (above) Axial SPECT slices are defined parallel to the brain long axis from occipital to prefrontal. For the Cortical Metabolic index (CMi), one or more axial slices are centered one third of the way from the top of the brain, just superior to the roof of the normal-sized lateral ventricles. Activity display uses a Sokoloff color scale, with white for peak brain, black for zero and spectral colors for intermediate activities. Computer-selected isocontours (see Fig. B) define areas that contain activity > a certain fraction of the peak activity. The 30% isocontour represents total brain activity in an axial slice, chosen slightly outside the actual external edge of the brain to correct for attenuation. The 60% isocontour approximates the cortex. The Cortical Metabolic index (CMi), the ratio of activity within the 60% isocontour to that within the 30% isocontour is a measure of cortical brain function. The Cortical Perfusion index (CPi) is similarly calculated from 60% and 30% isocontours after the patient receives a cerebral perfusion stimulant such as 0.5 to 1 g acetazolamide IV or 0.4 to 0.8 mg nitroglycerin sublingual. The difference between CPi and CMi is a measure of cerebral flow reserve (CFi).

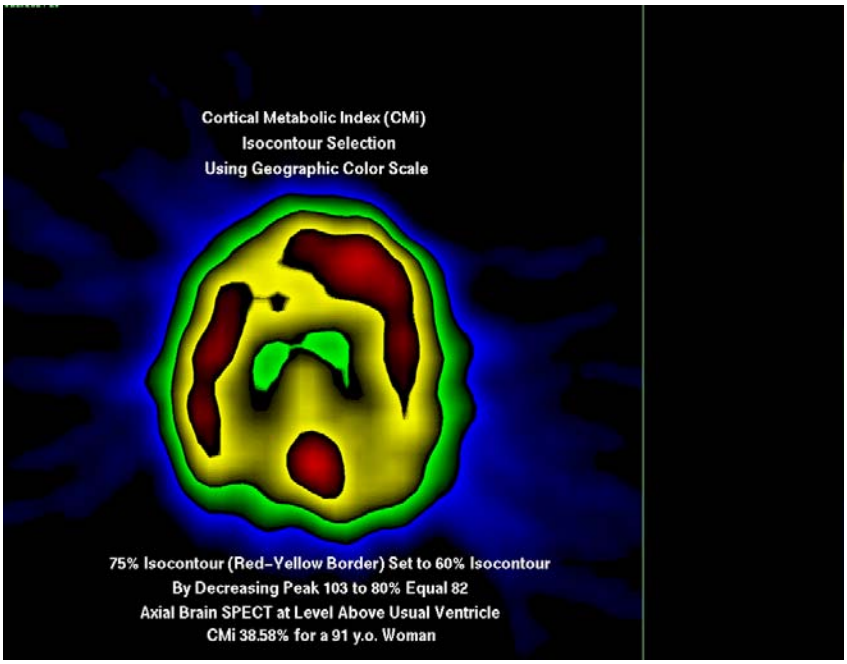

Fig. B. (above) The Cortical Metabolic index (CMi) 38.58%, for a 91 year-old moderately demented woman is demonstrated using a geographic color scale, similar to those available on nearly all commercial SPECT instruments. In 25 patients with low likelihood of disease the mean Cortical Metabolic index (performed with patients injected with metabolic (Tc-99m-ECD) or basal blood flow (Tc-99m-HMPAO) tracers is (57.60+-7.06)% and for CPi increases to (64.27+-7.04)%. The Cerebral Flow Reserve index CFi = CPi - CMi, (defined in low likelihood disease patients) is (6.67+-2.83)%. We found previously that abnormally decreased (95% confidence limit) CFi values < 1.06% are typical of patients with cerebrovascular or associated diseases such as hypertension, diabetes mellitus, insulin resistant syndrome, oxidative metal exposure and traumatic brain injury. For 74 patients with pituitary disease and neurological complaints CFi (–4.03+-4.94) was also low ($p < 0.001$).

1.

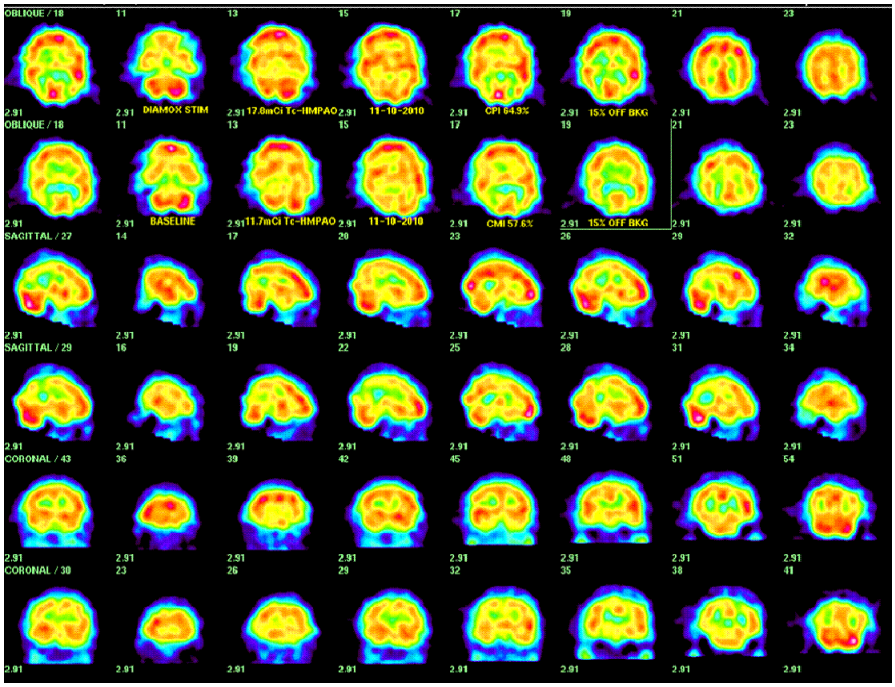

Fig 1: (above) To the right are brain SPECT images, acetazolamide (Diamox) 500 mg IV stimulated, shown in the top of three paired rows of images, over basal images, shown on the bottom of three paired rows of images. The patient is a 56 year-old African American woman post subtotal thyroidectomy for multinodular goiter, euthyroid on replacement l-thyroxine and with menopausal symptoms treated by estradiol. Her CMi 57.7% and CPi 64.9% are within normal limits (57.6+-14.1)% for CMi and (64.3+14.1)% for CPi among 25 patients with low likelihood of disease. Clinical complaints among these patients included migraine headache, patients with minor depression and a practicing physician with concern about possible minor memory impairment. No neurologic events were observed in these patients with an average follow-up of at least two years and several of them had repeat scans demonstrating stable or improving cortical indices. Repeated evaluations without intervening therapy or neurological clinical events typically were within a standard error of 3% in individual patients. The standard error of recalculation of CMi and CPi by trained technologists is < 0.5%.

2.

Demographic Summary	Number Of Patients
Sex / Age	
Female / Male (ratio) = 1.667	325 /195
Mean Age (54.3+-14.9) Years ± Std; Age Range 20.2 to -97.7 years	520
Race	
All Patients: 78.5% White 21.5% Others*	520
Pituitary Patients: 84.2% White; 15.8% Others*	101
Low Disease Likelihood Patients: 17 F, 8 M Mean Age: (52.6+-16.5) years	25
Cerebral Flow Reserve index **Mean (CFi)** = CPi - CMi = **(6.67+-2.83)%**	

Key Concepts

Cerebral flow reserve analysis by isocontour activity ratios (a fractal geometric method, cf. Fig A and Fig B to the left, under Abstract Text) predicts stroke risk in most patients.

2) Renal Disease, which changes the brain arterial input function, requires correction to calculated Cerebral Flow Reserve (CFi).

3) Nonlinear dependence of regional cerebral perfusion tracer uptake on tracer concentration and flow is likely and may explain inecreased CFi vs. expected invariance with linear differential effects and fractal methods.

4) Both dynamic and delayed metabolic effects (e.g. diabetic hyper-or hypoglycemia with or without incretin therapy, hypo- or hypertension, drug dependent or not) may contribute to perfusion or metabolic tracer cerebral uptake and cause negative CFi values.

5) Remarkably, a correction term to subtract from CFi that gives a reasonable fit to the data **(see Panel 5)** for both positive and negative CFi values is given by a simple linear relation to estimated GFR:

C = 9 - 0.10(GFR)

Where C is the correction factor to subtract from CFi for patients with estimated GFR in ml/min per 1.72 square meter body surface area.

Stroke Risk Groups	Number of Patients
Low Disease Likelihood Patients: 17 F, 8 M Mean Age: (52.6+-16.5) years **Cerebral Flow Reserve index** **Mean (CFi)** = CPi - CMi = **(6.67+-2.83)%**	25
Pituitary Patients Total Atrial Fibrillation 4.0%	4/101
Untreated Pituitary Patients (Pd) Age (53.8+-14.6) **Mean CFi = (-5.64+-4.88)%**	73
27.4% Stroke	20/73
5.5% TIA	4/73
Treated Pituitary Patients (Pd) Age (51.8+-15.6) **Mean CFi = (4.34+-6.17)%**	44
18.2% Stroke	8/44
6.8% TIA	3/44
Renal Disease (Rd) Age (63.7+-12.3) **Mean CFi = (-0.83+-7.14)%**	95
13.7% Stroke	
21.1% TIA	14/95
(GFR < 60 ml/min; Cystatin C > 0.85 mg/L)	20/95
Hypertensive (BP) Without Rd Age (54.5+-14.4) **Mean CFi** = **(0.12+-7.69)%**	183
12.0% Stroke	22/183
9.3% TIA	17/183
Traumatic Brain Injury (TI) Age (50.7+-15.1) **Mean CFi** = **(-0.04+-6.71)%**	106
16.0% Stroke	17/106
4.7% TIA	5/106

Diabetes mellitus including Rd Age (57.5+-13.6)	218
65.6% of Diabetics Hypertensive	143/218
Mean CFi = **(0.47+-8.56)%**	
13.3% Stroke	29/218
6.4% TIA	14/218
Insulin Resistant Nondiabetics Age (55.1+-13.9)	85
Mean CFi = (-0.92+-7.69)%	
9.4% Stroke	8/85
8.2% TIA	7/85
Thyroid Disease (TD)	107
Mean CFi = (0.82+-7.0)%	
4.7% Stroke	5/107
2.8% TIA	3/107
4.7% Autoimmune Encephalopathy	5/107

3.

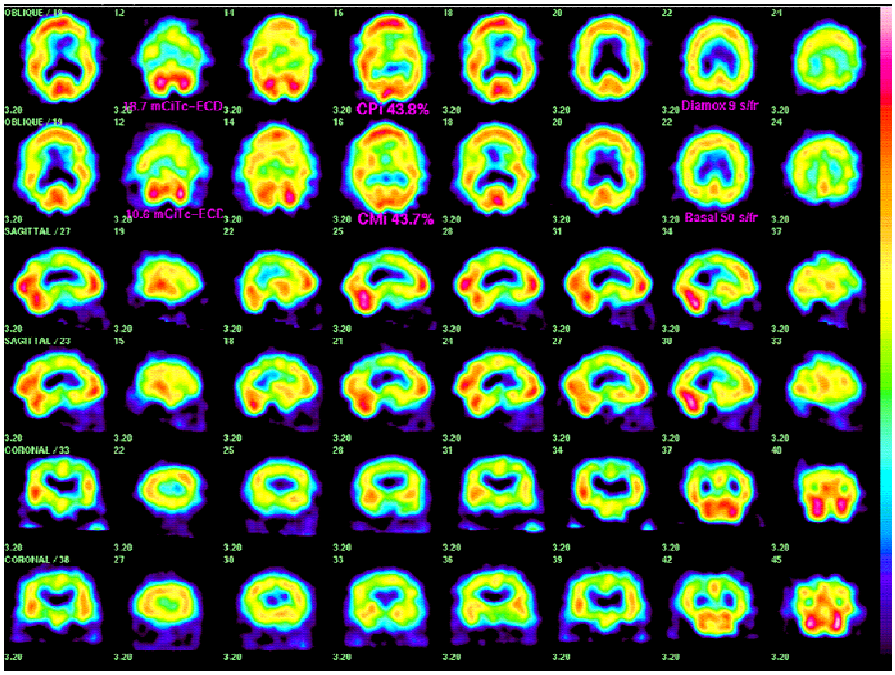

Fig 3a: (above) Brain SPECT was performed rapidly for an 86 year-old hypertensive man (initial untreated BP at age 84 yrs was 174/94) with short-term memory loss had rapid protocol Brain SPECT shown to the right. Tc-99m-ECD behaves as a perfusion tracer during the initial approx 3 min and has stable Cerebral activity after 1 min allowing a rapid perfusion SPECT (Top of each of 3 paired rows of images). After 40 min the pattern from the same tracer is dominated by energy-dependent metabolic fixation of the tracer (Bottom of each of 3 paired image rows). The cerebral flow reserve (CFi) in this patient is 1.1%, near the lower limit of normal 1.06% and similar to the mean CFi (0.12+-7.69)% noted in 183 hypertensive patients with neurological complaints who did not have renal disease. Including 67 hypertensive patients with renal disease did not change CFi significantly (0.16+-8.02)%. **The incidence of strokes in hypertensive patients without Rd was 22/184 or 12.0% and increased to**

39/250 or 15.6% among all hypertensives when those with Rd were included.

By one year after the SPECT scan shown, despite well-controlled hypertension, the patient developed insulin resistant syndrome, confirmed by HbA1c 5.8%.

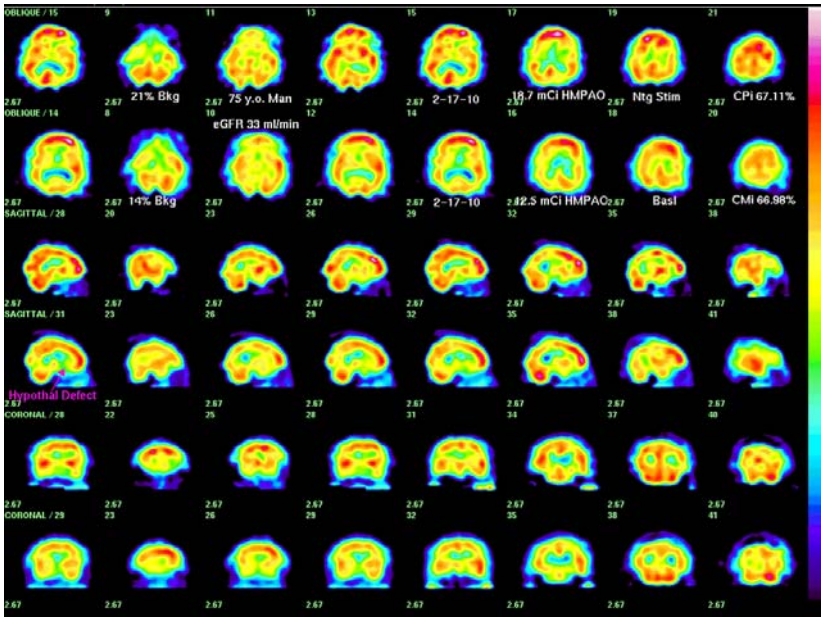

Fig 3b: (above) Brain SPECT on the right used 0.8 mg nitroglycerin sublingual for perfusion-stimulated images (top row of each of 3 paired image rows; basal images are on the bottom) in a 75 year-old hypertensive man with relatively stable renal insufficiency: serum crea-tinine in the last 2 years 1.60 to 2.25 mg/dL, and near the time of imaging, 2.14 mg/dl, corresponding to GFR 33.9 ml/min. The patient has Mild Cognitive Impairment and cerebral flow reserve (CFi) 67.11 - 66.98 = 0.13%, abnormal vs. >1% expected. Realizing that renal disease (Rd) artifactually increases CFi in comparison to other patients with similar stroke risk, such as pituitary patients, we realized (American Association of Clinical Endocrinology, San Diego, May, 2011) that a nonlinear correction to the relation between flow and CPi was necessary for Rd. **We discovered empirically that a linear correction to the relation of GFR from the MDRD equation and a correction to CFi, viz.c = 0.10(GFR) - 9.0, where c is the correction for CFi, provided a good fit to the data. With this correction CFic = - 5.48 instead of +0.13%, similar to the mean CFi (-5.77+-4.97)% for 73 untreated pituitary patients. Overall among 95 Rd patients mean CFi (-1.27+-6.91)% correlated with 14/95 or 14.7% of Rd patients with stroke vs. 20/73 or 27.4% strokes among untreated Pd. Interestingly**, this patient has a hypothalamic deficit (magenta arrow) similar to that seen in many pituitary patients.

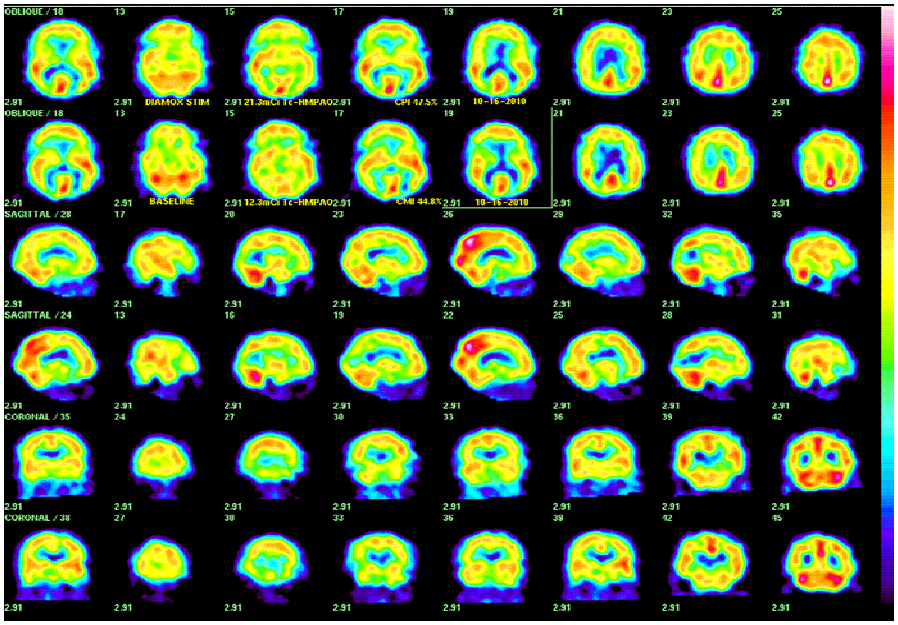

Fig: 4a: (above) A 46 year-old chronic pain patient with multiple osteoporotic thoracic spine fractures requires morphine sulfate 400 mg total daily oral dose and is pan hypopituitary, requiring testosterone, thyroid and adrenal replacement. His TYM test 46 of 50 is within normal limits (scores < 42 are consistent with cognitive impairment) as was MRI of the pituitary including dynamic images with contrast. His SPECT scan on the right shows acetazolamide stimulated perfusion (top of each of 3 paired rows of images) over basal images (bottom of each of 3 paired rows). The Cerebral Flow Reserve index CFi, is given by CPi 47.5% minus CMi 44.8% = 2.6%, at least one standard deviation below the mean CFi = 6.56+-2.83. Findings include prominent ventricles consistent with functional cerebral atrophy more prominent than expected at age 46 years, orbitofrontal hypoperfusion, evident in each of the first saggital images (17 perfusion-stimulated and 3 basal), patchy basal ganglia activity (saggital images 26 and 22), right mesial temporal (coronal 33) and inferior temporal (coronal 39) hypoperfusion, bilateral posterior parietal hypoperfusion (axial image 19) and wedge-shaped occipital hypo-perfusion mainly in the stimulated images (saggital 29). Perfusion-stimulated cerebral ischemia is likely from this finding and consistent with risk of stroke which may affect the visual cortex. Subjectively, the patient did have evidence of right homonymous hemianopia. Pituitary disease (Pd) as a consequence of chronic opiate therapy is increasingly recognized and was a possible factor in 22/74 or 30% of untreated Pd in this series.

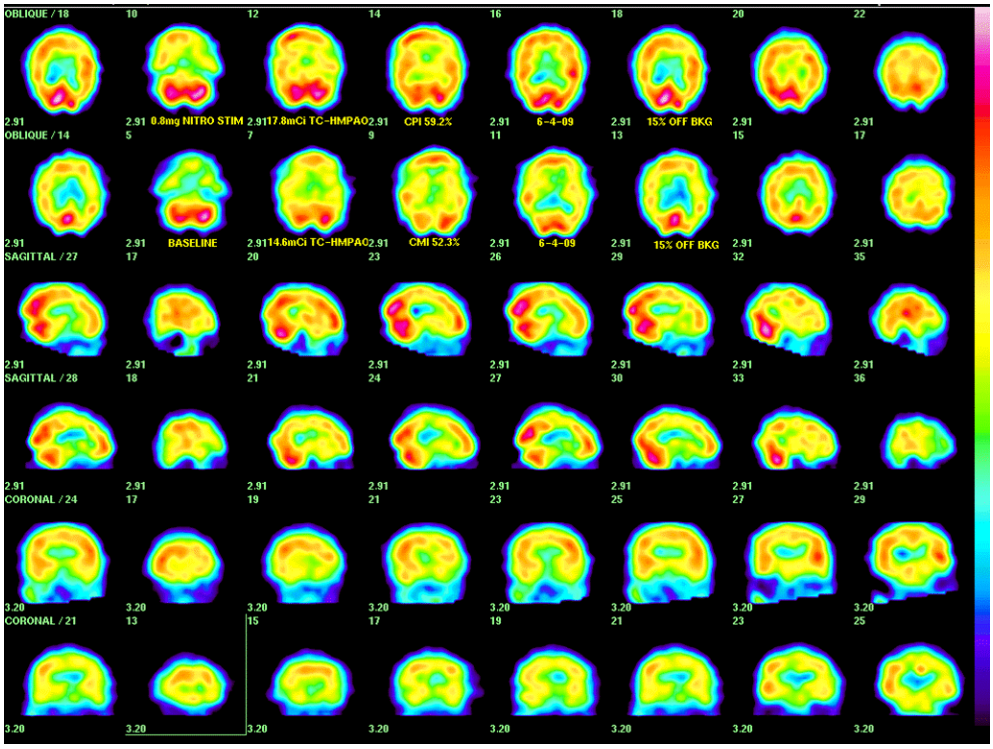

Fig. 4b: (above) A 75.6 year-old Caucasian woman with serum creatinine 1.80 mg/dl,GFR 29 ml/min complains of memory loss, dizziness and chronic back pain requiring chronic opiate therapy. Her MMSE is 25/30 and TYM 49/50. Without correction for renal insufficiency, her CFi (59.2 - 52.3)% = 6.9% is normal. With a flat correction of 3.0% used prior to this study (more applicable to earlier stage Rd) it remains normal, at 3.9%. With the new equation for GFR dependence her CFi corrects to 0.8%, which is abnormal (< 1%). Hypothalamic hypoperfusion is noted in mid saggital and coronal images below.

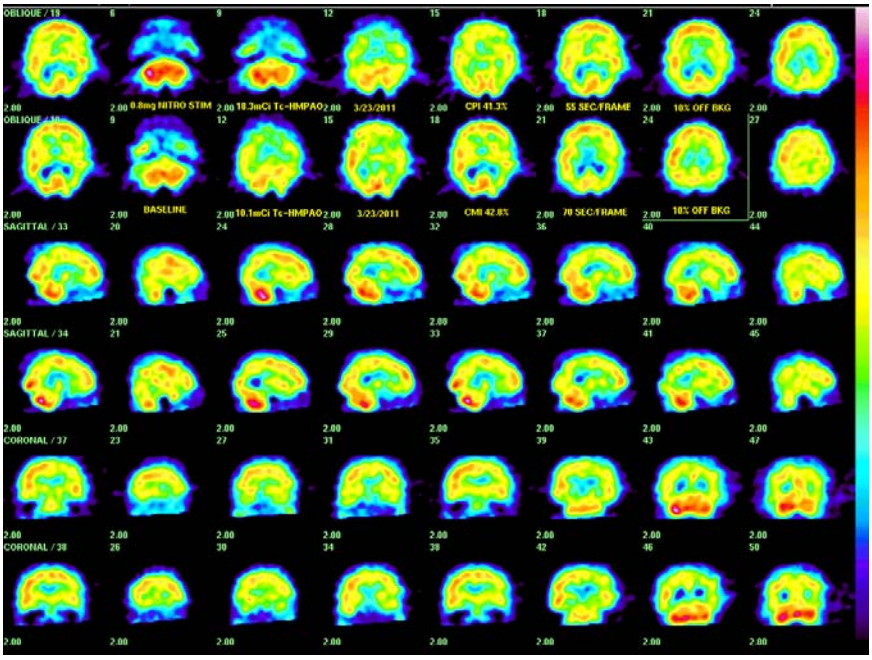

Fig 4c: (above) Follow-up brain SPECT for the now 77.4 year old woman of Fig 4b shows compromised CMi 47.8% and CPi 41.3% with FRi –6.5% (corrected –13.7%) after her serum creatinine increased to 2.80 mg/dl, GFR 18 ml/min and her TYM decreased to 45, consistent with progressive memory loss. A new left parietal deficit (saggital 32) and patchy temporal deficts (coronals 27-34) suggest progressive cerebrovascular disease and orbitofrontal deficits (lateral saggital images) suggest associated psychiatric depression.

5.

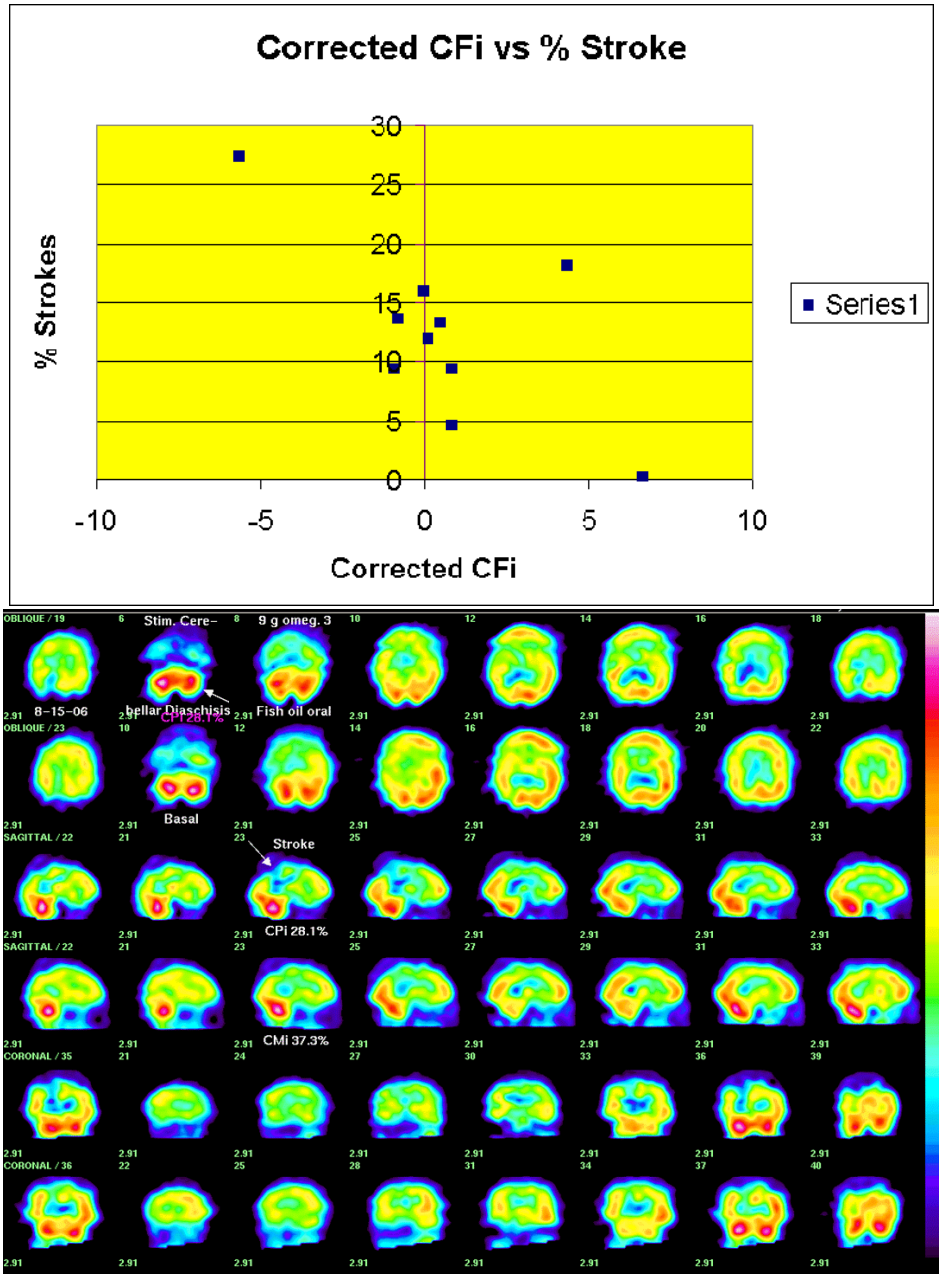

Fig. 5a: Below is SPECT for an 86 year-old woman with renal failure, serum creatinine 2.6 mg/dl, cystatin C 2.75 mg/L, and GFR 22 ml/min, exemplifies exception to the usual preservation of FRi with renal failure which is usually observed prior to stroke. The top row of each set of 3 paired images is post perfusion stimulation, using 10 g of fish oil in this case, which we have repeatedly shown is similar to either acetazolamide IV or nitroglycerin sublingual. A right posterior parietal stroke is easily appreciated. Saggital image 23 shows further decreased perfusion in the penumbra area as compared to the basal images below.

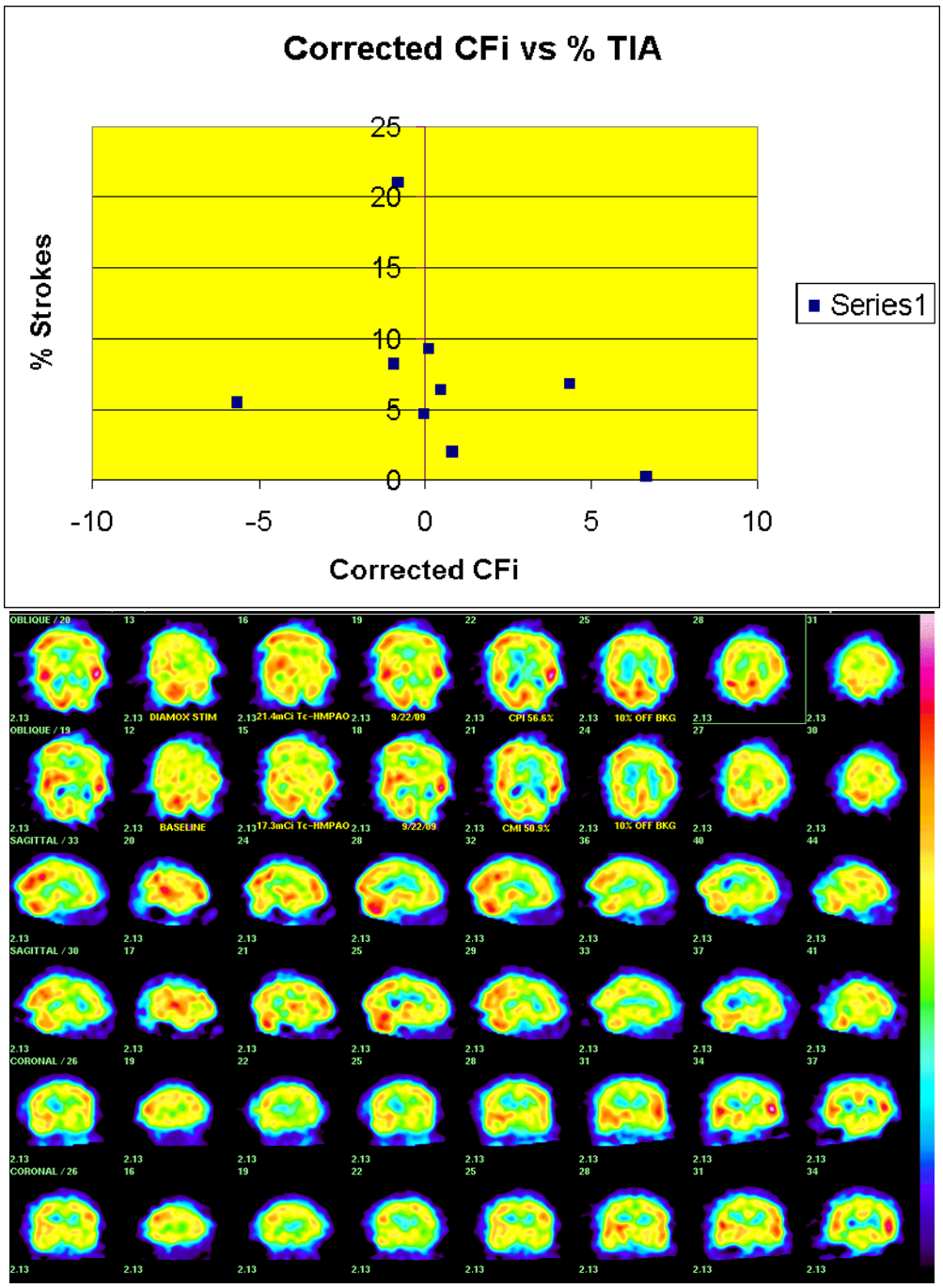

Fig 5b: (above) Positive Effect of Incretin Therapy: A 56 year-old hypertensive, type 2 diabetic woman with memory loss (MMSE 26/30; TYM 29/50) had Cmi 50.1% and Cpi 44.2% (abnormal Cfi - 5.9%) on baseline brain SPECT. Follow-up brain SPECT after two years, shown below, shows Cmi 50.9% and Cpi 56.6% with normal Cfi 5.7%, cf. low liklelihood of disease patients Cfi (6.67+-2.83)% after control of hyopertension with aliskirin (Tekturna), hyperlipidemia with atorvistatin (Lipitor) and glycemic control (for two years) with exenatide (Byetta).

Stroke prophylaxsis in this patient was cilostazol 100 mg oral twice daily. Her memory also improved and TYM increased from 29/50 to 34/50.

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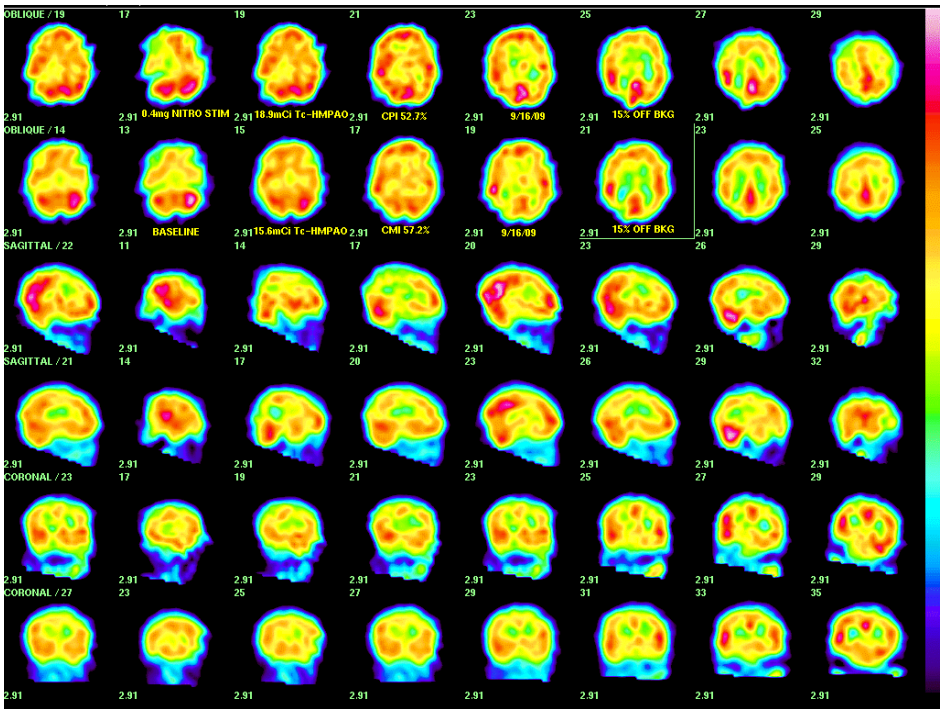

Fig. 6a: (above) A 44 year-old insulin-resistant (IRS) woman with hypertriglyceridemia and difficulty controlling her weight suffers from migraine and syncopal spells after a motor vehicle accident. She has borderline stage 3 renal insufficiency with glomerular filtration rate 56 ml/min at the time of brain SPECT shown on the right which shows minor abnormalities including a wedge-shaped right frontal defect (axial 29), posterior right parietal minor deficit (Axial 25) and decreased cerebral flow reserve index, CFi = 52.7% - 57.2% = - 4.5% (normal > 1.0%). Correction of CFi for renal insufficiency would make CFi even more abnormal, approx. –7.5%.

Values of CPi significantly less than CMi are not likely from first order linear differential effects which predict more similar values of CPi and CMi. One hypothesis to explain these results is that cerebral tracer extraction at higher flow rates is nonlinear (decreases more than proportionate with high flow rates) and hence, if cerebral flow is pushed to higher levels by decrease in flow to other organs, then the CPi results will be significantly lower; however, in order to explain negative values for CFI another mechanism is necessary. Our data from chronic as well as dynamic studies suggests that metabolic disease inhibits cerebral tracer fixation in a nonlinear way, resulting in disproportionate decrease in CPi and negative CFi values. Remarkably, a simple linear transformation of GFR is directly proportional to stroke risk among patients with related metabolic conditions. (Cf. Key Concepts in panel 2).

Abnormal CFi is seen in about 65% of patients with IRS, similar to diabetics (reported previously in The International Vascular Dementia Conference,

Barcelona, Spain, 2009).

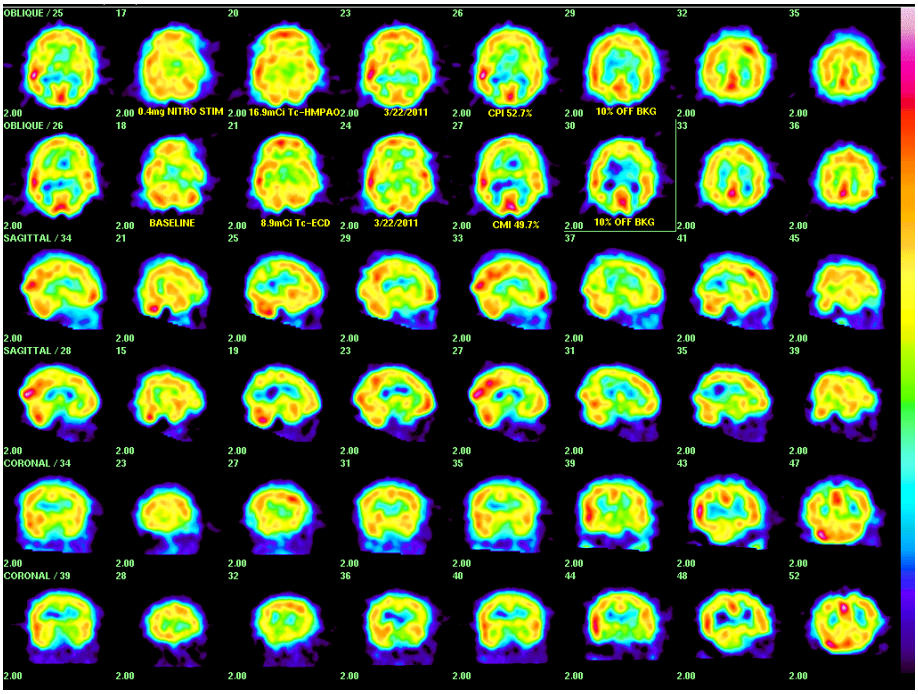

Fig. 6b: The same, now 46 year-old woman whose brain SPECT was shown above (Fig. 6a) is involved in a more serious motor vehicle accident (combined impact speed > 50 miles/hr) and although she does not recall losing consciousness, suffers acceleration-deceleration traumatic brain injury (TBI) accompanied by a post concussion syndrome, with exacerbation of migraine headache, difficulty concentrating and lightheadedness. She also has even more difficulty with controlling her weight and often gains several pounds within a week. Although TBI patients often show abnormality more prominently in perfusion-stimulated brain SPECT, this patient's basal study (bottom row of 3 paired image rows to the right) shows more prominent basal ganglia abnormality, patchy temporal deficits, bilateral posterior parietal and patchy periventricular hypoperfusion. Her renal function at the time of the follow-up study is normal. Use of Tc-99m-ECD, which more closely mirrors F-18 fludoexyglucose determined cerebral metabolism, for the follow-up basal study may also have enhanced recognition of subtle metabolic abnormalities. Initial evaluation of pituitary function in this patient was normal, although **in the present series of patients with neurological complaints, 46/107 or 43.0% of TBI patients had at least one abnormal (inappropriate) pituitary hormone level.**

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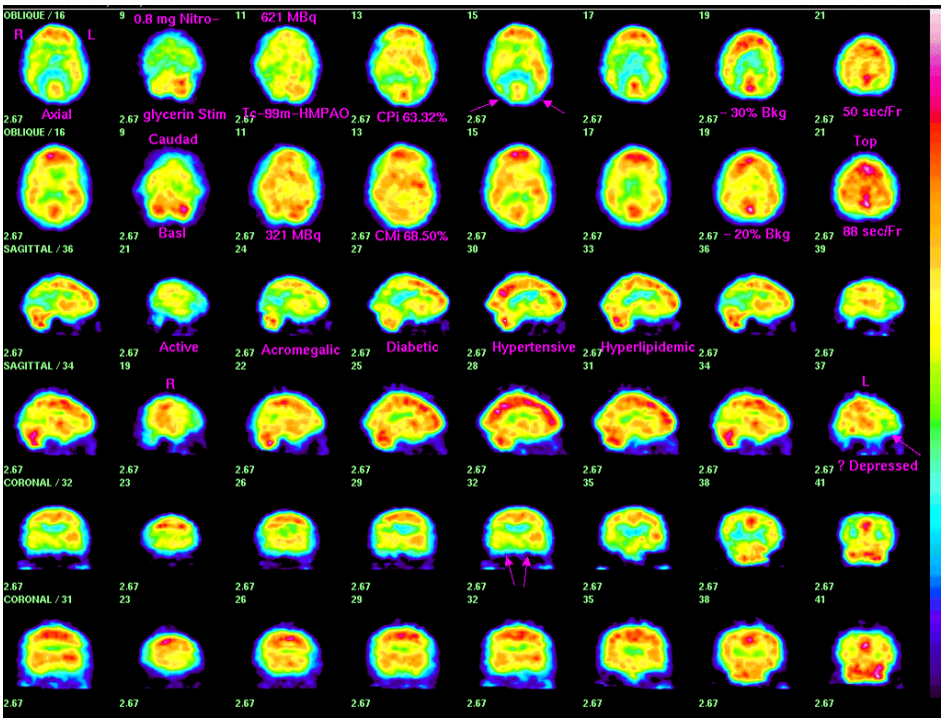

Fig. 7a: (above) Acromegalic 62 year-old man, post hypophysectomy, with persistant pituitary tumor activity documented by incompletely suppressed somatomedian C (Insulin-Like Growth Factor 1) 283 ng/ml (normal 76-212 ng/ml) by Somatulin therapy has mild cognitive impairment (short-term memory loss requiring frequent notes) and renal insufficiency: serum creatinine 1.61 mg/dl and GFR 44 ml/min. Multiple metabolic risk factors including active pituitary disease, hypertension, type 2 diabetes mellitus and hyperlipidemia appear to overcome the usual effect of renal insufficiency to preserve CR, which is abnormal here since CPi 63.32% minus CMi 68.50% << 3%. Peak contribution of the basal image to the nitroglycerin-stimulated SPECT is 20%; however, only 10% additional background is subtracted beyond a scattering background taken as 20% here, which emphasizes bilateral parieto-occipital and mesial temporal deficits typical of amnestic mild cognitive impairment.

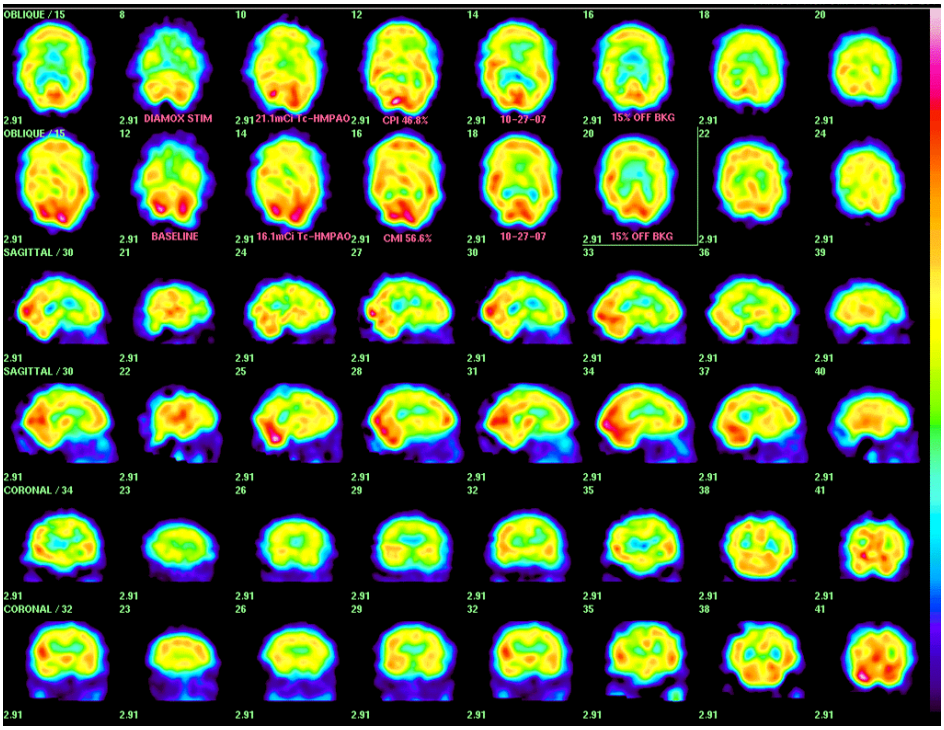

Fig.7b: (above) SPECT images for a 71 year-old hypogonadal, type 2 diabetic man with hypothalamic hypoperfusion and stable renal insufficiency, GFR (46.4+-3) ml/min over 2 years, whose CR (46.8-56.6)% < 3 is also abnormal. Of a total of 4 pituitary patients with renal insufficiency, 75% (3/4) were exceptions to the usual observation of normal CR, these 3 together with 10 scans in 8 stroke patients (one of whom had pituitary apoplexy) accounting for 13/19 = 68.4% of the total number of such atypical cases.

Both this patient and the pituitary patient shown in Fig. 7a (above, left) have small left orbitofrontal deficits (arrow above, saggital image 37) and above, in Fig. 7b in saggital images 36, 39 which may be associated with depression, these two correlated in 80.4% or 37/46 of pituitary patients (at least 53.6%, 37/69 of whom were clinically depressed). Depression may thus be yet another stroke risk factor associated with regional cerebral hypoperfusion, and interrelated to other risk factors: cf the known strong associations of depression with stroke and with diabetes mellitus. We observed that depression-associated cerebral hypoperfusion, even in patients with history of resistant depression, may either resolve or be exacerbated acutely by incretin therapy, specifically pramlintide (Symlin) 90 mcg sq or exenatide 10 mcg sq, and that exenatide (Byetta) over 2 years improved cerebral flow reserve (Fig 5b).